PTO 08-7631

CC = CS
19911104
B1
272584

METHOD OF PREPARING BICYCLIC ANHYDRIDES OF DIETHYLENETRIAMINOPENTACETIC ACID AND ETHYLENEDIAMINOTETRACETIC ACID

[Způsob přípravy bicyklických anhdridů kyseliny diethylentriaminopentaoctové a kyseliny ethylenediaminotetroactové]

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UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. SEPTEMBER 2008
TRANSLATED BY: THE MCELROY TRANSLATION COMPANY

PUBLICATION COUNTRY	(19):	CS
DOCUMENT NUMBER	(10):	272584
DOCUMENT KIND	(13):	B1
LAID-OPEN TO PUBLIC INSPECTION	(40):	19900514
PUBLICATION DATE	(45):	19911104
APPLICATION NUMBER	(21):	PV4329-88.U
APPLICATION DATE	(22):	19880621
INTERNATIONAL CLASSIFICATION[5]	(51):	C 07 C 229/28
INVENTORS/APPLICANT	(72):	Budský František et al.
TITLE	(54):	METHOD OF PREPARING BICYCLIC ANHYDRIDES OF DIETHYLENETRIAMINOPENTACETIC ACID AND ETHYLENEDIAMINOTETRACETIC ACID
FOREIGN TITLE	[54A]:	Způsob přípravy bicyklických anhdridů kyseliny diethylentriaminopentaoctové a kyseliny ethylenediaminotetroactové

The invention relates to a method of preparing cyclic anhydrides of aminopolycarboxylic acids, In particular, cyclic anhydrides of strong chelatons. All chelatons that contain one or more iminodiacetic – $N(CH_2COOH)_2$ groups in their molecule are suitable for said preparation of cyclic anyhydrides. These groups form cyclic anhydrides of the $-N(CH_2CO)_2O$ type by the reactions described below. Chelatons of the following type are particularly involved: iminodiacetic, nitrilotriacetic, ethylenediaminotetracetic, diethylenetriaminopentacetic acids and their derivatives. Cyclic anhydrides thus prepared can be used for conjugation reactions with proteins, especially with monoclonal and polyclonal antibodies. Antibodies conjugated with a strong chelaton can then be labeled with metal radionuclides of suitable physical characteristics (for example, $111_{In,}$ $90_{Y,}$ $99m_{Tc}$ and the like) and be used for the treatment and diagnosis in vivo of serious diseases.

A method of preparing a bicyclic anhydride of diethylenetriaminopentacetic acid by the action of the acetic anhydride in a pyridine medium or merely in an acetic anhydride medium with catalysis by pyridine is known. The reactions proceed at a temperature of 65°C for 24 h.

The shortcomings of this method are eliminated by the method of preparing cyclic anhydrides of aminopolycarboxylic acids by the action of acetic anhydride on the initial aminopolycarboxylic acid deprived of all metal cations in a medium of dioxane and pyridine under the catalytic action of N-dimethyl-4-aminopyridine at 70°C. The reaction time is thus shortened to 8 h with a yield of 100%. According to the method of further use, the preparation is either isolated by filtration or is left in the form of a suspension in dioxane.

Example 1

The following reaction constituents are placed in a mixing reaction vessel at a temperature of 70°C:

diethylenetriaminopentacetic acid (DTPA) 39.3 g

anhydrous a.p. dioxane 85 mL

anhydrous a.p. pyridine 20 mL

a.p. acetic anhydride 25 mL

N-dimethyl-4-aminopyridine 1 g

The reaction mixture is intensively stirred for 8 h at a temperature of 70°C, then cooled to laboratory temperature, and the resulting bicyclic anhydride of diethylenetriaminopentacetic acid (cDTPAA), which is insoluble in the given medium, is decanted 3 times with 40 mL of anhydrous dioxane. After the last decantation, the volume is adjusted with dioxane to 1000 mL and the resulting suspension has a cDTPAA concentration of 0.1 mol/L if there were no losses during decantation. Identification and determination of the concentration are done with the aid of infrared spectra and with the titration methods described below. Infrared spectrum: the original DTPA presents valence vibrations of the carbonyl group at the wave number of 1695 and 1732 cm^{-1}, while cDTPAA is at 1819 and 1774 cm^{-1}. cDTPAA also has a strong absorption band of the C-O-C valence vibrations at 1108 cm^{-1}.

Titration method: 0.1 mmol of cDTPAA suspended in dioxane is measured out and the suspension is dissolved while boiling in 15 mL of anhydrous methanol. After 5 min of boiling, the solution is cooled and diluted with 15 mL of water. It is titrated with a volumetric solution of NaOl in the presence of 0.2 mmol of CA^{2+} with the aid of glass electrodes. Under these conditions the titration equivalent is 3 for cDTPAA, while it is 5 for DTPA.

Example 2

The following reaction constituents are placed in a mixing reaction vessel at a temperature of 70°C:

ethylenediaminotetracetic acid (EDTA) 29.4 g

anhydrous a.p. dioxane 85 mL

anhydrous a.p. pyridine 20 mL

a.p. acetic anhydride 25 mL

N-dimethyl-4-aminopyridine 1 g

The preparation method is completely in accordance with Example 1, but the bicyclic anhydride of ethylenediaminotetracetic acid (cEDTAA) results. In infrared spectrometry, the original EDTA presents an absorption band of the valence vibrations of the carbonyl group at 1695 cm^{-1} while cEDTAA is at 1808 and 1761 cm^{-1}. The absorption band of the valence vibrations C-O-C is at 1071 cm^{-1}. In conducting titration, the titration equivalent is 2 and 4 respectively.

Claim

Method of preparing bicyclic anhydrides of diethylenetriaminopentacetic acid and ethylenediaminotetracetic acid by the action of acetic anhydride on said acids deprived of all metal cations, characterized in that the reaction proceeds in a medium of dioxane and pyridine under the catalytic action of N-dimethyl-4-aminopyridine at 70°C for 8 h.